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ВСЕМИРНАЯ ОРГАНИЗАЦИЯ ИНТЕЛЛЕКТУАЛЬНОЙ СОБСТВЕННОСТИ

CERTIFICATION

It is hereby certified that the attached copy is a true copy of the record copy of International Application No. PCT/EP02/08062, filed with the European Patent Office as receiving Office on 25 June 2002 and received by the International Bureau on 06 September 2002, including any pages containing corrections and/or rectifications transmitted by the competent Authority to, and received by, the International Bureau before the completion of the technical preparations for international publication.

By: The International Bureau

Judith Zahra
Head
PCT Processing Service

Date: 03 July 2003 (03.07.03)

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP02/08062

International Application No.

International Filing Date 25 JUN 2002 (25.06.2002)

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 025079 PCT - CD

Box No. I TITLE OF INVENTION

Thiazine and oxazine derivatives as MMP-13 inhibitors.

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WARNER-LAMBERT COMPANY

201 Tabor Road
Morris Plains, NJ 07950
UNITED STATES OF AMERICA

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GAUDILLIERE Bernard
28 rue de Zilina
FR - 92000 NANTERRE
FRANCE

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HIRSCH Denise
PFIZER
Global Research and Development
Fresnes Laboratories, 3-9 rue de la Loge, B.P. 100
94265 FRESNES CEDEX
FRANCE

Telephone No. 33 1 40 96 32 00

Facsimile No. 33 1 40 96 76 90

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

JACOBELLI Henry
65 avenue du Général de Gaulle
F - 91550 PARAY VIEILLE POSTE
FRANCE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

See Notes to the request form

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZM** Zambia, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH & LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, **TR** Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GQ** Equatorial Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AG** Antigua and Barbuda
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan .....
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **BZ** Belize .....
☒ **CA** Canada
☒ **CH & LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CO** Colombia
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
☒ **DZ** Algeria .....
☒ **EC** Ecuador .....
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **HR** Croatia .....
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **MZ** Mozambique
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **OM** Oman
☒ **PH** Philippines .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TN** Tunisia
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZM** Zambia
☒ **ZW** Zimbabwe .....

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ ..... ☐ ..... ☐ .....
☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided,* ***the space is insufficient*** *to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

(i) ***if more than two persons are to be indicated as applicants and/or inventors*** *and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

(ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication* ***"the States indicated in the Supplemental Box"*** *is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

(iii) *if, in Box No. II or in any of the sub-boxes of Box No. III,* ***the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America****: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

(iv) *if, in addition to the agent(s) indicated in Box No. IV, there are* ***further agents****: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

(v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "****patent of addition****," or "****certificate of addition****," or if, in Box No. V, the name of the United States of America is accompanied by an indication "****continuation****" or "****continuation-in-part****": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

(vi) *if, in Box No. VI, there are* ***more than five earlier applications whose priority is claimed****: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If, with regard to the* ***precautionary designation statement*** *contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

Continuation of Box IV:

DUFRESNE Guillaume
LAURENT Claire
DEKKER Henricke

Pfizer
Global Research and Development
Fresnes Laboratories, 3-9 rue de la Loge, B.P. 100
94265 FRESNES CEDEX
FRANCE

Continuation of Box V:

and any other state which have become party to the PCT after issuance of this sheet.

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor :	
☒ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	1
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☒ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	1
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

In relation to the international application

WARNER-LAMBERT COMPANY is entitled to apply for and be granted a patent by virtue of the following:

WARNER-LAMBERT COMPANY is entitled as employer of the inventors,

GAUDILLIERE Bernard, 28 rue de Zilina, F - 92000 NANTERRE, FRANCE
JACOBELLI Henry, 65 avenue du Général de Gaulle, F - 91550 PARAY VIEILLE POSTE, FRANCE.

This declaration is made for the purposes of all designations, except the designation of the United States of America.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

Box No. VIII (iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America)

The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No.VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of inventorship (Rules 4.17(iv) and 51*bis*.1(a)(iv)) for the purposes of the designation of the United States of America:

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/ ..... (if furnishing declaration pursuant to Rule 26*ter*).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: .....

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: GAUDILLIERE Bernard

Residence: NANTERRE, FRANCE
(city and either US state, if applicable, or country)

Mailing Address: 28 rue de Zilina
F - 92000 NANTERRE, FRANCE

Citizenship: French

Inventor's Signature: .....
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: 25 June 2002
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: JACOBELLI Henry

Residence: PARAY VIEILLE POSTE, FRANCE
(city and either US state, if applicable, or country)

Mailing Address: 65 avenue du Général de Gaulle
F - 91550 ~~LONGJUMEAU~~, FRANCE PARAY VIEILLE POSTE

Citizenship: French

Inventor's Signature: .....
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: June 25, 2002
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)".

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains:**

(a) the following number of **sheets in paper form:**

request (including declaration sheets)	:	8
description (excluding sequence listing part)	:	26
claims	:	15
abstract	:	1
drawings	:	
Sub-total number of sheets	:	50
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	50

(b) sequence listing part of description filed in **computer readable form**

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney	:	1
3. ☒ original general power of attorney	:	1
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☐ other *(specify)*:	:	

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

HIRSCH Denise
Professional Representative
before the European Patent Office

For receiving Office use only

1. Date of actual receipt of the purported international application: 25 JUIN 2002 (25. 06. 2002)

2. Drawings:
☐ received:
☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau: 06 SEP 2002

TITLE OF THE INVENTION

Thiazine and oxazine derivatives as MMP-13 inhibitors.

FIELD OF THE INVENTION

The present invention relates to novel thiazine and oxazine derivatives which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

TECHNOLOGICAL BACKGROUND OF THE INVENTION

Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

In pathological situations, an irreversible degradation of articular cartilage takes place, as is the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

There is a need in the prior art for novel MMP inhibitors, more particularly for MMP-13 inhibitors, in order to prevent and/or correct the imbalance in the renewal of extracellular matrix tissue, such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPD), age-related macular degeneration (ARMD) and cancer.

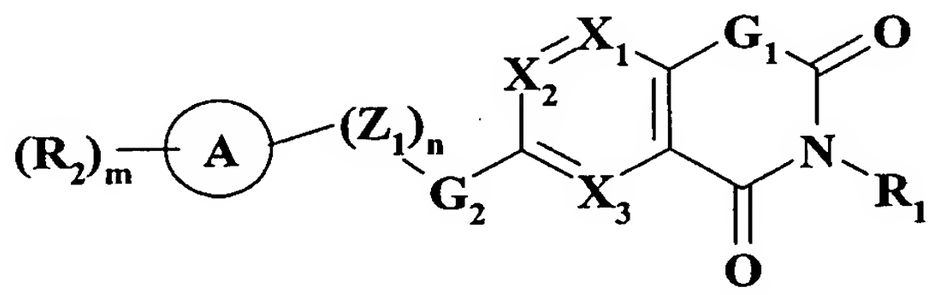
MMP-inhibitor compounds are known. Most of these MMP-inhibitors are not selective for a single MMP, such as those described by Montana and Baxter (2000) or by Clark et al. (2000).

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating pathologies associated with the destruction of the extracellular matrix and with cancer.

SUMMARY OF THE INVENTION

The applicant has identified novel thiazine and oxazine derivatives that are matrix metalloprotease inhibitors, and more specifically compounds that are selective MMP-13 inhibitors.

More specifically, the present invention relates to compounds of formula (I) :



(I)

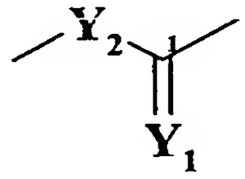
wherein:

- X_1, X_2, and X_3, independently of each other, represent a nitrogen atom or a group $-CR_3$ in which R_3 represents a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, amino, mono$(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, hydroxy, $(C_1\text{-}C_6)$alkoxy, and halogen,

with the proviso that not more than two of the groups X_1, X_2 and X_3 simultaneously represent a nitrogen atom,

- G_1 represents an oxygen atom or a group $S(O)_p$ in which p represents an integer from 0 to 2 inclusive,

- G_2 represents a group selected from carbon-carbon triple bond, C=O, C=S, $S(O)_q$ in which q represents an integer from 0 to 2 inclusive, or a group of formula (i/a):



(i/a)

in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents a group selected from oxygen, sulphur, -NH and -N(C_1-C_6)alkyl, and Y_2 represents a group selected from oxygen, sulphur, -NH and -N(C_1-C_6)alkyl,

- n represents an integer from 0 to 6 inclusive,

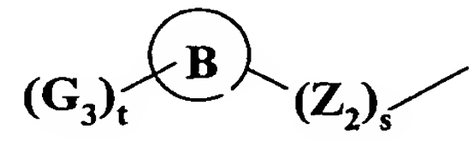
- Z_1 represents -CR_4R_5, wherein R_4 and R_5, identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, -OR_6, -SR_6, and -C(=O)OR_6, in which R_6 is hydrogen atom or (C_1-C_6)alkyl, and

- wherein when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one to two isolated or conjugated multiple bonds,

- and/or wherein when n is greater than or equal to 2 one of said -CR_4R_5 may be replaced with a group selected from oxygen, $S(O)_r$ in which r represents an integer from 0 to 2 inclusive, -NH and -N(C_1-C_6)alkyl,

- A represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

- R_1 represents a group selected from :
  - hydrogen,
  - (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, these groups may be optionally substituted with one or more groups, which may be identical or different independently of each other, selected from amino, cyano, trihalogeno(C_1-C_6)alkyl, cycloalkyl, $-C(=O)NR_7R_8$, $-C(=O)OR_7$, OR_7, and SR_7, in which R_7 and R_8, which may be identical or different independently of each other, represent hydrogen or (C_1-C_6)alkyl,
  - and the group of formula (i/b) :



(i/b)

✓ in which s is an integer from 0 to 8 inclusive,

✓ Z_2 represents $-CR_9R_{10}$ wherein R_9 and R_{10}, identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, phenyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, OR_6, SR_6 and $-C(=O)OR_6$ in which R_6 is as defined hereinbefore, and

- wherein when s is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or two isolated or conjugated multiple bonds,
- and/or wherein when p is greater or equal to 2, one of said $-CR_9R_{10}$ may be replaced with a group selected from oxygen, $S(O)_u$ in which u is an integer from 0 to 2 inclusive, -NH, $-N(C_1-C_6)$alkyl, and carbonyl,

✓ B represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

✓ t is an integer from 0 to 7 inclusive,

✓ the group(s) G_3, which may be identical or different independently of each other, is (are) selected from (C_1-C_6)alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{11}R_{12}$,

$-N(R_{11})C(=O)R_{12}$, $-N(R_{11})C(=O)OR_{12}$, $-N(R_{11})SO_2R_{12}$, $-N(SO_2R_{11})_2$, $-OR_{11}$, $-S(O)_{k1}R_{11}$, $-SO_2-N(R_{11})-(CH_2)_{k2}-NR_{12}R_{13}$, $-(CH_2)_kSO_2NR_{11}R_{12}$, $-X_4(CH_2)_kC(=O)OR_{11}$, $-(CH_2)_kC(=O)OR_{11}$, $-C(=O)O-(CH_2)_{k2}-NR_{11}R_{12}$, $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{14}$, $-X_4(CH_2)_kC(=O)NR_{11}R_{12}$, $-(CH_2)_kC(=O)NR_{11}R_{12}$, $-R_{15}-C(=O)OR_{11}$, $-X_5-R_{16}$, and $-C(=O)-R_{17}-NR_{11}R_{12}$ in which :

- X_4 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by a hydrogen or a (C_1-C_6)alkyl group,

- k is an integer from 0 to 3 inclusive,

- k1 is an integer from 0 to 2 inclusive,

- k2 is an integer from 1 to 4 inclusive,

- R_{11}, R_{12} and R_{13}, which may be identical or different independently of each other, are selected from hydrogen and (C_1-C_6)alkyl,

- R_{14} represents a group selected from (C_1-C_6)alkyl, $-R_{17}-NR_{11}R_{12}$, $-R_{17}-NR_{11}-C(=O)-R_{17}-NR_{12}R_{13}$, and $-C(=O)O-R_{17}-NR_{11}R_{12}$ in which R_{17} represents a linear or branched (C_1-C_6)alkylene group, and R_{11}, R_{12} and R_{13} are as defined hereinbefore,

- R_{15} represents a (C_3-C_6)cycloalkyl group,

- X_5 represents a group selected from a single bond, $-CH_2-$, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,

- R_{16} represents a group selected from :

  - a 5- or 6-membered monocyclic aryl or heteroaryl, which is optionally substituted by one or more groups, which may be identical or different independently of each

other, selected from (C_1-C_6)alkyl, halogen, hydroxy, cyano, tetrazolyl, amino, and -C(=O)OR_7 wherein R_7 represents hydrogen or (C_1-C_6)alkyl,

- and a 5- or 6-membered monocyclic cycloalkyl or heterocycloalkyl, which is optionally susbstituted by one or more groups, which may be identical or different indepently of each other, selected from (C_1-C_6)alkyl, halogen, hydroxy, oxo, cyano, tetrazolyl, amino, and -C(=O)OR_7 wherein R_7 represents hydrogen or (C_1-C_6)alkyl,

- m is an integer from 0 to 7 inclusive,

- the group(s) R_2, which may be identical or different independently of each other, is (are) selected from (C_1-C_6)alkyl, halogen, -CN, -NO_2, -SCF_3, -CF_3, -OCF_3, -NR_7R_8, -OR_7, -SR_7, -SOR_7, -SO_2R_7, -$(CH_2)_kSO_2NR_7R_8$, -$X_7(CH_2)_kC(=O)OR_7$, -$(CH_2)_kC(=O)OR_7$, -$X_7(CH_2)_kC(=O)NR_7R_8$, -$(CH_2)_kC(=O)NR_7R_8$, and –X_8-R_{18} in which:

  - X_7 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,

  - k is an integer from 0 to 3 inclusive,

  - R_7 and R_8, which may be identical or different independently of each other, are selected from hydrogen and (C_1-C_6)alkyl,

  - X_8 represents a group selected from single bond, -CH_2-, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,

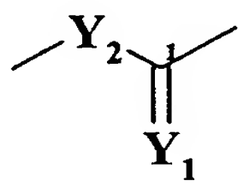
  - R_{18} represents a group selected from phenyl, a 5- or 6-membered monocyclic, heteroaryl, and a 5- or 6-membered monocyclic cycloalkyl, each of these groups being optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C_1-C_6)alkyl, halogen, hydroxy and amino,

and optionally, their racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts,

and with the proviso that the compound of formula (I) is not 6-(2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine)-benzoate, 6-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine and 6-(2,4-dihydroxy)-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine.

According to a first embodiment, the invention relates to compounds of formula (I) wherein :

- G_1 represents a sulphur atom,
- G_2 represents a group of formula (i/a):



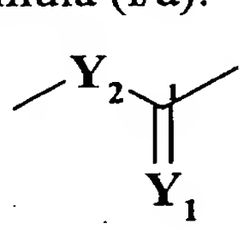
(i/a)

in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- X_1, X_2, X_3, n, Z_1, A, R_1, m and R_2 are as defined in formula (I).

According to a second embodiment, the invention relates to compounds of formula (I) wherein :

- G_1 represents an oxygen atom,
- G_2 represents a group of formula (i/a):



(i/a)

in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- X_1, X_2, X_3, n, Z_1, A, R_1, m and R_2 are as defined in formula (I).

According to a third embodiment, the invention relates to compounds of formula (I) wherein :

- G_1 represents a sulphur atom,
- G_2 represents a carbon-carbon triple bond,

- n represents an integer from 1 to 6 inclusive,

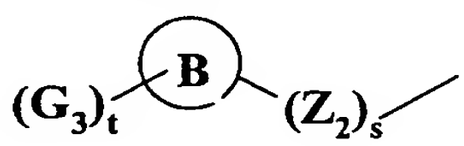
X_1, X_2, X_3, Z_1, A, R_1, m and R_2 are as defined in formula (I).

According to a fourth embodiment, the invention relates to compounds of formula (I) wherein :

- G_1 represents an oxygen atom,
- G_2 represents a carbon-carbon triple bond,
- n represents an integer from 1 to 6 inclusive,

X_1, X_2, X_3, Z_1, A, R_1, m and R_2 are as defined in formula (I).

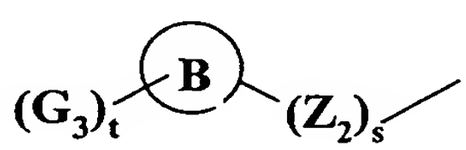
The substituent R_1 that is preferred according to the invention is the group of formula (i/b):



(i/b)

wherein Z_2, s, B, G_3 and t are as defined in the compound of formula (I).

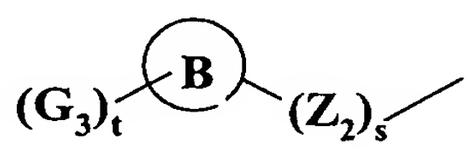
More particularly, the substituent R_1 that is preferred according to the invention is the group of formula (i/b):



(i/b)

wherein Z_2 represents a group $-CR_9R_{10}$ in which R_9 and R_{10} represents each a hydrogen atom, s is equal to one, and B, G_3, and t are as defined in the compound of formula (I).

More particularly, the substituent R_1 that is preferred according to the invention is the group of formula (i/b):



(i/b)

wherein B represents a phenyl group, t is equal to 0 or 1, and G_3, when it is present, represents a group selected from OR_{11}, halogen, and $(CH_2)_kC(=O)OR_{11}$ in which R_{11} represents an hydrogen atom or a $(C_1$-$C_6)$alkyl group and k is equal to zero.

Preferred compounds of the invention are compounds of formula (I) wherein X_1 represents a group $-CR_3$ in which R_3 represents a hydrogen atom, X_2 represents a nitrogen atom or a

group $-CR_3$ in which R_3 represents a hydrogen atom, and X_3 represents a group $-CR_3$ in which R_3 represents a hydrogen atom.

Advantageously, preferred compounds of the invention are those compounds of formula (I) wherein Z_1 represents $-CR_4R_5$ in which R_4 and R_5 represent each a hydrogen atom, and n is equal to one.

Especially preferred compounds of the invention are compounds of formula (I) wherein A represents a group selected from phenyl and pyridyl, m is equal to zero or one, and R_2 represents a (C_1-C_6)alkoxy group or a hydrogen atom.

Another especially preferred compounds of the invention are compound of formula (I) wherein A represents an imidazolyl group.

More particularly, the invention relates to the following compounds of formula (I) :

- 3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]thiazine-6-carboxylic acid 4-methoxy benzylamide;
- 3-(4-methoxybenzyl)2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine-6-carboxylic acid 4-methoxybenzylamide;
- and 4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1,3-benzothiazin-3-ylmethyl]-benzoic acid.

The optical isomers, the N-oxides, as well as the addition salts with a pharmaceutically-acceptable acid or base, of the preferred compounds form an integral part of the invention.

The invention also relates to a pharmaceutical composition comprising as active ingredient an effective amount of a compound of formula (I) together with one or more pharmaceutically-acceptable excipients or carriers.

Another embodiment of the invention concerns the use of the compound of formula (I) for the preparation of a medicinal product intended for treating a disease involving therapy by

inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease.

The invention also relates to a method for treating a living body afflicted with a disease involving a therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient in need thereof.

A preferred method of treatment according to this invention is treatment of a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases, age-related degeneration and cancers.

More particularly, a preferred method of treatment according to this invention is treatment of disease selected from arthritis, osteoarthritis and rheumatoid arthritis.

DETAILED DESCRIPTION OF THE INVENTION

The compounds provided by this invention are those defined in formula (I). In formula (I), it is understood that :

- a (C_1-C_6)alkyl group denotes a linear or branched group containing from 1 to 6 carbon atoms ; example of such groups, without implying any limitation are methyl, ethyl, propyl, isopropyl, tert-butyl, neopentyl, hexyl,
- a (C_2-C_6)alkenyl group denotes a linear or branched group containing from 2 to 6 carbon atoms, and one or more double bonds ; examples of such groups without implying any limitation are vinyl, allyl, 3-buten-1-yl, 2-methyl-buten-1-yl, hexenyl,
- a (C_2-C_6)alkynyl group denotes a linear or branched group containing from 2 to 6 carbon atoms, and one or more triple bonds ; examples of such groups without implying any limitation are ethynyl, propynyl, 3-butyn-1-yl, 2-methyl-butyn-1-yl, hexynyl,

- a (C_1-C_6)alkoxy group means the alkyl group as mentioned above bound through an oxygen atom ; examples of such compounds without implying any limitation are methoxy, ethoxy, *n*-propyloxy, *tert*-butyloxy,
- a mono(C_1-C_6)alkylamino denotes a amino group substituted by one (C_1-C_6)alkyl group as defined hereinbefore ; example of such groups, without implying any limitation are methyl amino, isobutyl amino, ethylamino,
- a di(C_1-C_6)alkylamino denotes a amino group substituted by two (C_1-C_6)alkyl groups as defined hereinbefore, each alkyl group being identical or different ; example of such groups, without implying any limitation are dimethylamino, diethylamino,
- an aryl group denotes an aromatic monocyclic or bicyclic system containing from 5 to 10 carbon atoms, and in the case of a bicyclic system, one of the ring of which is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated ; examples of such groups without implying any limitation are, phenyl, naphthyl, indenyl, benzocyclobutenyl,
- a heteroaryl group denotes an aryl group as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen ; examples of such groups without implying any limitation are furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzofuryl, benzothienyl, indolyl, quinolyl, isoquinolyl, imidazolyl, benzodioxolyl, benzodioxinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl,
- a cycloalkyl group denotes a monocyclic or bicyclic system containing from 3 to 10 carbon atoms, this system being saturated or partially unsaturated but without aromatic character ; examples of such groups without implying any limitation are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cycloheptyl, adamantyl, decalinyl, norbornyl,
- a heterocycloalkyl group denotes a cycloalkyl group as defined hereinbefore in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur, and nitrogen,
- a bicycle denotes two fused-monocycle or two bridged-monocycle,
- a trihalogeno(C_1-C_6)alkyl group denotes an alkyl group as defined above which contains a trihalogeno group ; examples of such groups without implying any limitation are trifluoromethyl, 2,2,2-trifluoroethyl,

- a (C_1-C_7)acyl group denotes an alkyl group or an aryl group as defined above bound through a carbonyl group ; examples of such groups without implying any limitation are acetyl, ethylcarbonyl, benzoyl,
- a multiple bond denotes double bond or triple bond,
- a halogen atom means fluoro, chloro, bromo or iodo,

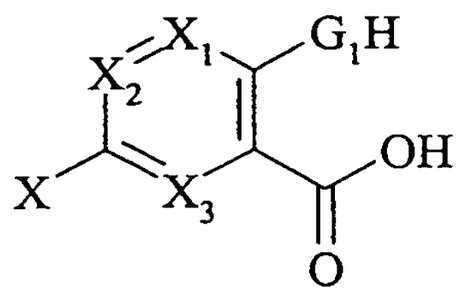
optical isomers refer to racemates, enantiomers and diastereoisomers.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in *J. Pharm. Sci.*, 1977, 66, 1-19.

Pharmaceutically acceptable acids mean non-toxic mineral or organic acids. Among those there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, nitric acid, citric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, ascorbic acid, oxalic acid, methanesulfonic acid, camphoric acid, benzoic acid, toluenesulfonic acid, etc...

Pharmaceutically acceptable bases mean non-toxic mineral or organic bases. Among those, there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, calcium hydroxide, triethylamine, tert-butylamine, dibenzylethylenediamine, piperidine, pyrrolidine, benzylamine, quaternary ammonium hydroxides etc...

The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):



(II)

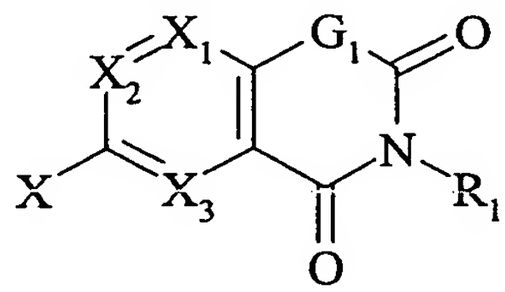
in which X_1, X_2, X_3, and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesyslate, tosylate and SO_2alkyl,

compound of formula (II) which is treated in basic medium with an isocyanate compound of formula (III):

$$R_1\text{-NCO} \quad \text{(III)}$$

in which R_1 has the same definitions as the compound of formula (I),

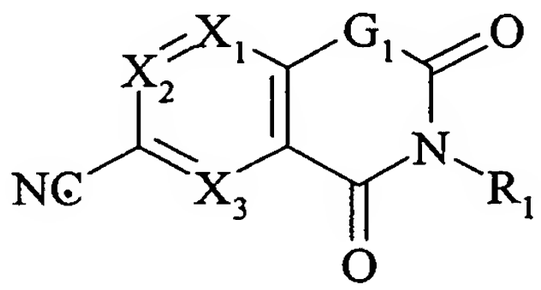
to yield the compound of formula (IV) :



(IV)

in which X_1, X_2, X_3, G_1, X, and R_1 are as defined hereinbefore,

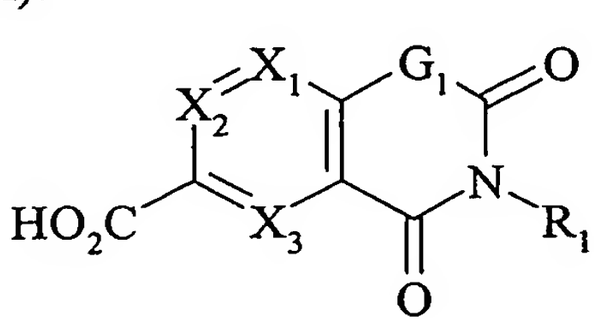
compound of formula (IV) in which the leaving group X is reacted with a cyanocuprate to yield the compound of formula (V) :



(V)

in which X_1, X_2, X_3, G_1, and R_1 are as defined hereinbefore,

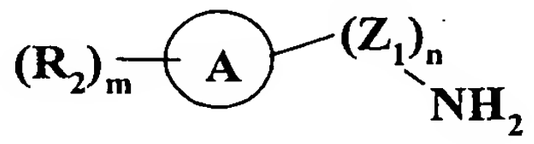
which compound of formula (V) is treated with an acid like sulfuric acid to yield the compound of formula (VI):



(VI)

in which X_1, X_2, X_3, G_1, and R_1 are as defined hereinbefore,

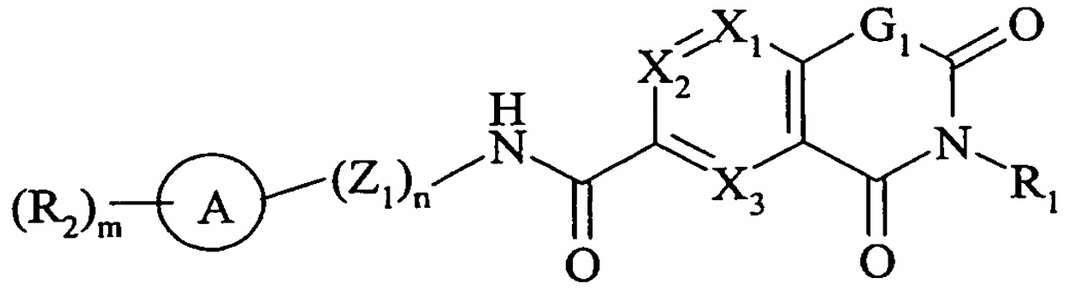
compound of formula (VI) which is treated with a compound of formula (VII):



(VII)

in which Z_1, R_2, A, n and m have the same definitions as the compound of formula (I),

by activating the acid function with an activator, in the presence of diisopropylethylamine and a solvent, to yield the compound of formula (I/a) which is a particular case of the compounds of formula (I):

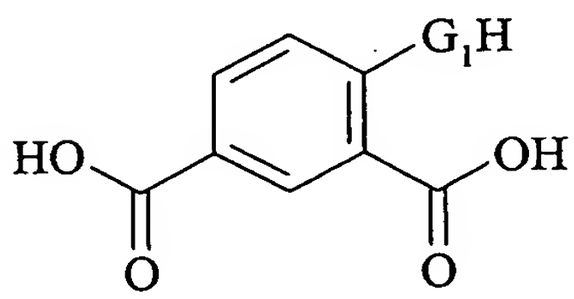


(I/a)

in which X_1, X_2, X_3, G_1, Z_1, R_1, R_2, A, n and m are as defined hereinbefore,

compounds of formula (I/a) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

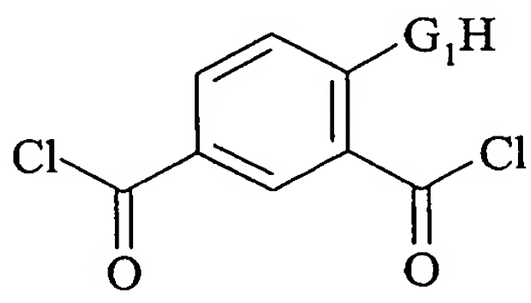
The invention also relates to another process for the preparation of specific compounds of formula (I/a), which are a particular case of compounds of formula (I),
which uses as starting material a compound of formula (II/A):



(II/A)

in which G_1 has the same definitions as the compound of formula (I),

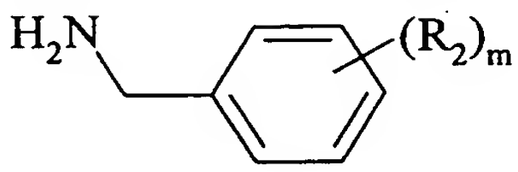
compound of formula (II/A) which is treated with $SOCl_2$ to yield the compound of formula (III/A) :



(III/A)

in which G_1 is as defined hereinbefore,

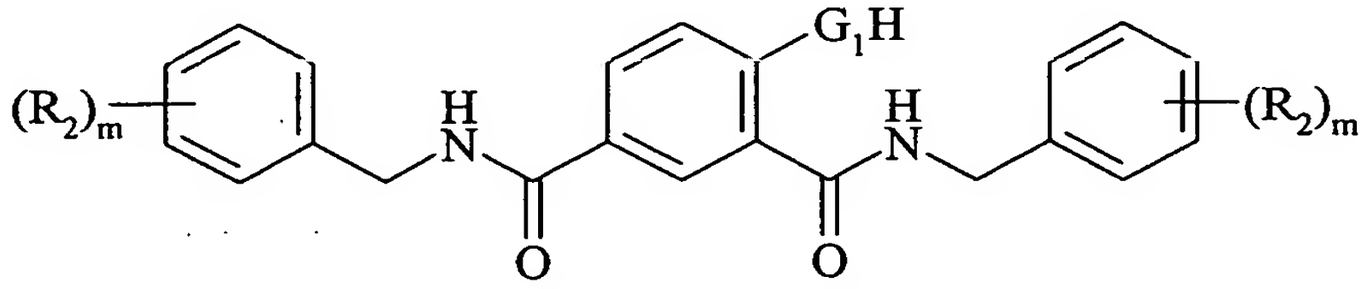
compound of formula (III/A) reacting with a benzylamine derivative of formula (IV/A):



(IV/A)

in which R_2 and m are as defined in the compound of formula (I),

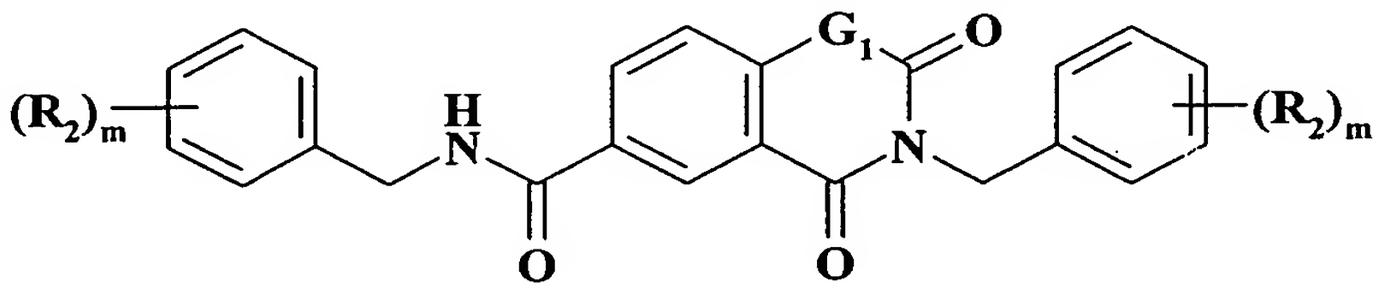
to yield the compound of formula (V/A):



(V/A)

in which G_1, m and R_2 are as defined hereinbefore,

compound of formula (V/A) reacting with a chloroformate compound, to yield the compound of formula (I/c) which is a particular case of the compounds of formula (I):

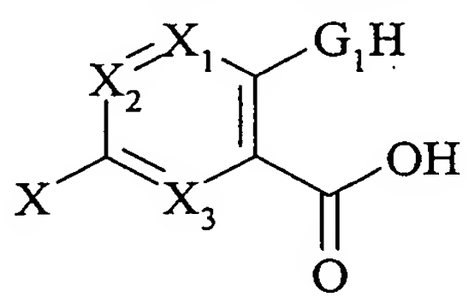


(I/c)

in which G_1, R_2 and m have the same definitions as the compound of formula (I),

compounds of formula (I/c) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

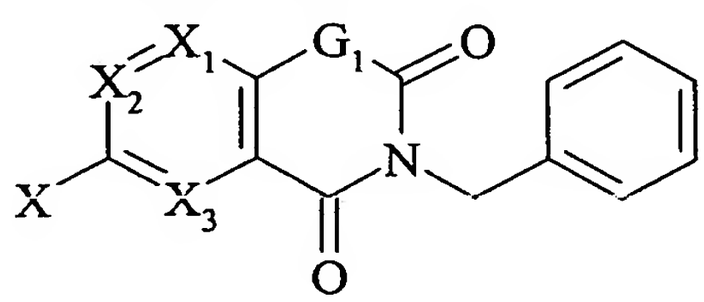
The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):



(II)

in which X_1, X_2, X_3, and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesyslate, tosylate and SO_2alkyl,

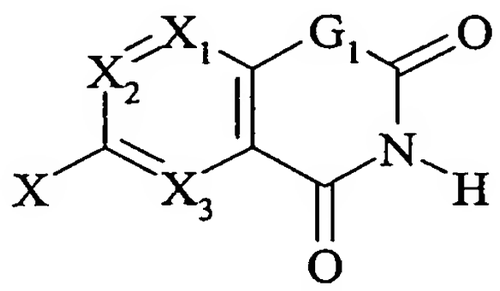
compound of formula (II) which is treated in basic medium with a benzylisocyanate to yield the compound of formula (VIII) :



(VIII)

in which X_1, X_2, X_3, G_1, and X are as defined hereinbefore,

compound of formula (VIII) which is treated with $AlCl_3$ in an apolar solvent to yield the compound of formula (IX) :



(IX)

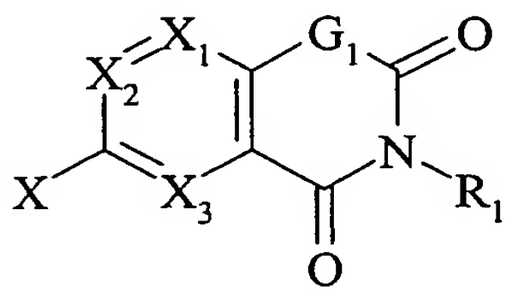
in which X_1, X_2, X_3, G_1, and X are as defined hereinbefore,

which compound of formula (IX) is treated in the presence of an inorganic base with a compound of formula (X):

R_1-X' (X)

in which R_1 is as defined in the compound of formula (I) and X' represents a leaving group like halogen atom, mesylate, tosyslate or triflate group,

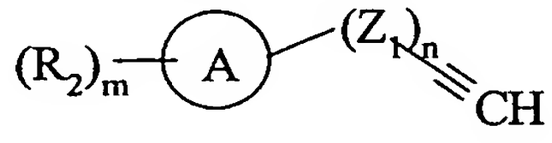
to yield a compound of formula (XI) :



(XI)

in which X_1, X_2, X_3, G_1, X and R_1 are as defined hereinbefore,

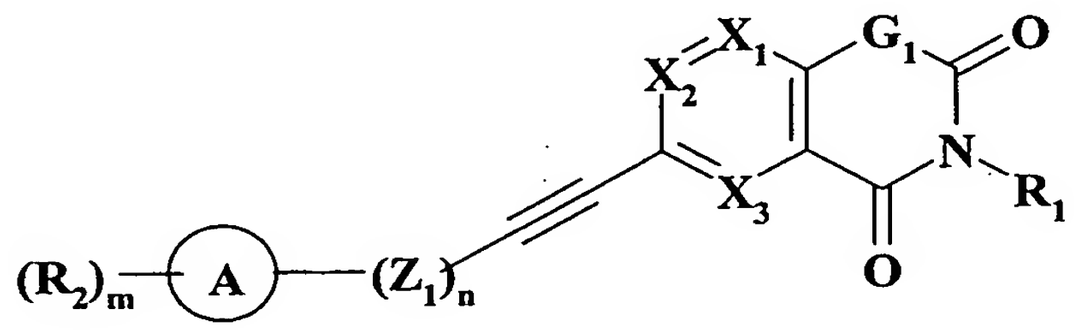
compound of formula (XI) which is condensed, in the presence of dichlorobis(triphenylphosphine)palladium, cupper iodide and *N,N'*-diisopropylethylamine in dimethylformamide, on a compound of formula (XII) :



(XII)

in which Z_1, R_2, A, n and m have the same definitions as the compound of formula (I),

to yield the compound of formula (I/b), which is a particular case of the compound of formula (I):

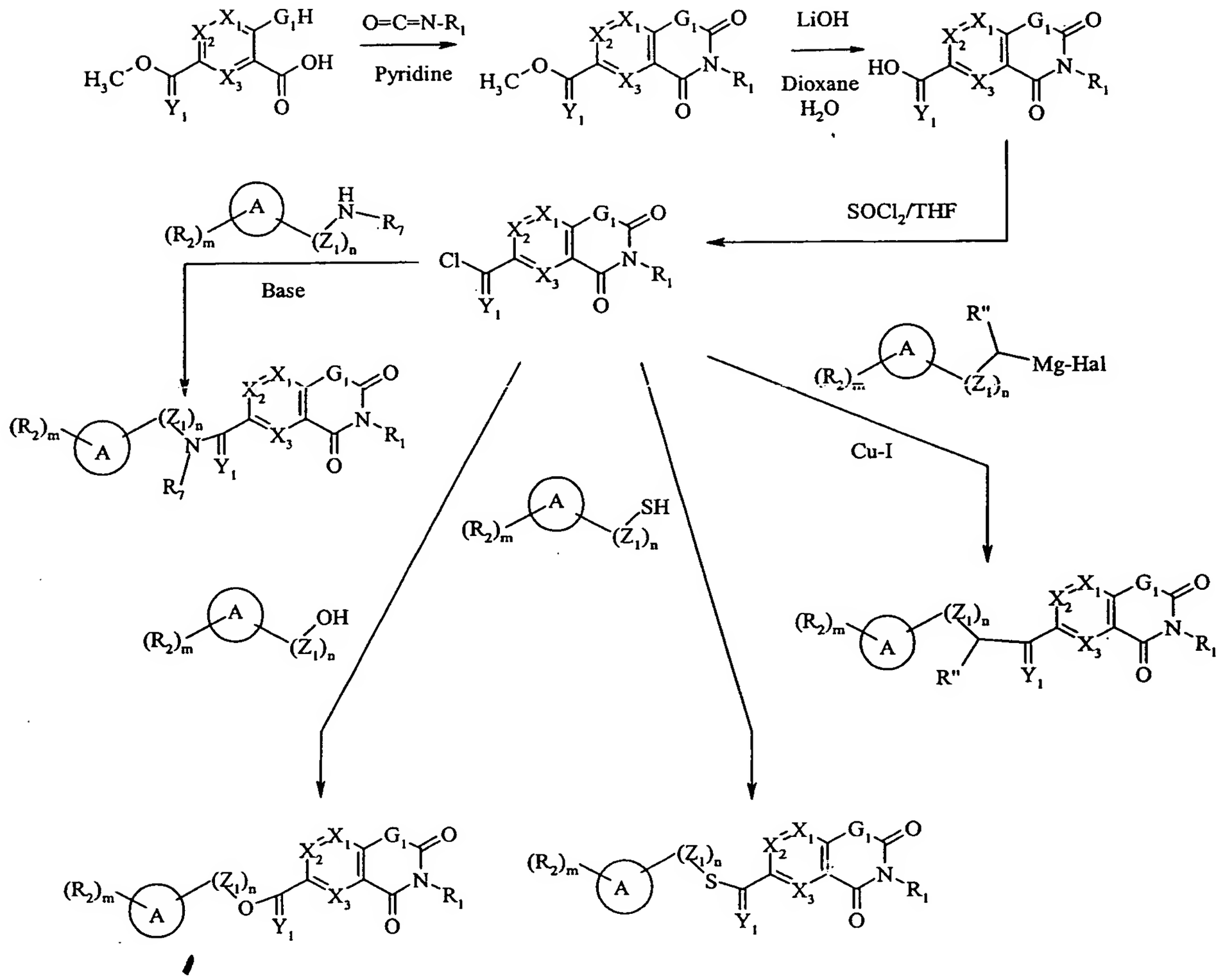


(I/b)

in which X_1, X_2, X_3, G_1, Z_1, R_1, R_2, A, n and m are as defined hereinbefore,

compounds of formula (I/b) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

A general process for the synthesis of the compounds of formula (I) is described in the following scheme:



in which R_7 is hydrogen or $(C_1\text{-}C_6)$alkyl, R'' is hydrogen or $(C_1\text{-}C_6)$alkyl, and R_1, R_2, G_1, X_1, X_2, X_3, A, Y_1, Z_1, n and m have the same meaning as that defined for the compound of formula (I).

The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

As mentioned above, compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13.

In this respect, their use is recommended for the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended for the treatment of any pathology in which destruction of extracellular matrix tissue occurs, and most particularly pathologies such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration and cancers.

The present invention also relates to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), an isomer thereof, a N-oxide thereof, or an addition salt thereof with a pharmaceutically-acceptable acid or base, alone or in combination with one or more pharmaceutically-acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspension and emulsions, and also sterile powders for reconstituting injectable solutions or dispersions.

Pharmaceutical compositions according to the invention for oral administration in solid form especially include tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules, for oral, nasal, buccal or ocular administration in liquid form, especially include emulsions, solutions, suspensions, drop, syrups and aerosols.

Pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration especially include powders, aerosols, creams, ointment, gels and patches.

The pharmaceutical compositions mentioned hereinbefore illustrate the invention but do not limit it in any way.

Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colorants, aromatizing agents etc...

The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 2 mg to 1 g per day in one or more administrations. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula (I)) and 40% to 99.5% by weight of pharmaceutically acceptable excipients or carriers.

The examples that follow illustrate the invention but do not limit it in any way.

The starting materials used are products that are known or that are prepared according to known operating procedures. The various preparations yield synthetic intermediates that are useful in preparation of the compounds of the invention. Some of these intermediates are new compounds.

The structures of the compounds described in the Examples and Preparations were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...)

In the Examples, it is understood that :

- DMSO means dimethylsulfoxide,
- TOTU means O-(ethoxycarbonyl)cyanomethylamino]-*N-N-N'-N'*-tetramethyl uronium fluoroborate,

EXAMPLES

Intermediate A : 3-benzyl-6-bromo-3,4-dihydro-benzothiazine-2,4-dione

A stirred suspension of 5-bromo-2-mercaptobenzoic acid (prepared after K. Sindelar and coll., Coll. Czech. Chem. Comm., 1988, 53 (2), 340) (8 g, 34.3 mmol) in pyridine (100 ml) was treated with benzyl isocyanate (4.3 ml, 34.3 mmol) and the mixture was heated at 105°C for 7 hours under a nitrogen atmosphere. Further benzyl isocyanate was added (4.3 ml) and the mixture heated at 105°C overnight under stirring. After cooling to room temperature, water was added until precipitation and the suspension stirred for 1 hour. The resulting precipitate was collected by filtration, washed several times with water and dried under high vacuum to give 11.5g (yield : 96%) of the entitled compound as a white amorphous solid.

Intermediate B : 3-benzyl-6-cyano-3,4-dihydro-benzothiazine-2,4-dione

CuCN (0.197g, 2.2 mmol) was added to a suspension of 3-benzyl-6-bromo-3,4-dihydro-benzothiazine-2,4-dione (intermediate A ; 0.35 g, 1.22 mmol) in N-methylpyrrolidone (4 ml) and the suspension obtained was heated at reflux under stirring for 2.5 hours. The solvent was removed under reduced pressure and the sticky residue obtained was stirred in a mixture of NH_4OH solution and dichloromethane. The organic phase was separated, washed with brine and dried over Na_2SO_4. The solvent was evaporated to afford 0.28 g of crude solid that was purified by chromatography on silica gel (cyclohexane 20/CH_2Cl_2 80) to give the entitled compound (0.15 g ; yield : 51%) as a white solid pure in TLC (cyclohexane 20 / CH_2Cl_2 80 ; Rf = 0.40).

Intermediate C : 3-benzyl-6-carboxy-3,4-dihydro-benzothiazine-2,4-dione

A suspension of 3-benzyl-6-cyano-3,4-dihydro-benzothiazine-2,4-dione (intermediate B ; 0.12 g, 0.4 mmol) in concentrated sulfuric acid (3 ml) and water (3 ml) was heated at reflux under stirring for 3 hours. After cooling to room temperature, water was added and the insoluble solid was collected by filtration, washed several times with water and dried

under high vacuum to give, after purification by chromatography on silica gel (CH_2Cl_2 95/methanol 5), 0.04g (yield : 31%) of the entitled compound as a white solid pure in TLC (CH_2Cl_2 90 / methanol 10 ; Rf = 0.30).

Intermediate D : 4-hydroxy-N,N'-bis[(4-methoxyphenyl)methyl]-1,3-benzenedicarboxamide

A mixture of 4-hydroxyisophthalic acid (2.0 g ; 11 mmol) in thionyl chloride (20 ml) and dimethylformamide (2 drops) was heated at reflux under stirring overnight. The excess of thionyl chloride was removed by evaporation and the residue dissolved into dichloromethane (100 ml).

After cooling, 4-methoxybenzylamine (6.8 g ; 50 mmol) was added in one portion and the mixture obtained was stirred at room temperature for 1 hour. The insoluble solid was separated by filtration and purified by chromatography on silica gel (CH_2Cl_2 95/methanol 5) to give 2.0 g of the entitled compound (yield : 43%) as a white solid pure in TLC (CH_2Cl_2 90/methanol 10 ; Rf = 0.70).

Intermediate E : 6-bromo-3,4-dihydro-benzothiazine-2,4-dione

Under an inert atmosphere, aluminium chloride (5.51 g, 41.3 mmol) was added in portions to a suspension of 3-benzyl-6-bromo-3,4-dihydro-benzothiazine-2,4-dione (intermediate A ; 2.4 g, 6.89 mmol) in benzene (50 ml) and the mixture obtained was heated at 50°C under stirring for 2 hours. After cooling, the mixture was poured into iced water, the precipitated product was filtrated after 1 h standing, washed several times with water until neutral pH, dried and finally triturated in dichloromethane then dried under high vacuum to give 1.5 g (yield : 84%) of the entitled compound pure in TLC (CH_2Cl_2 ; Rf = 0.10).
NMR H^1 (DMSO) δ (ppm) : 5.5(s, 2H); 7.25-7.35 (m, 3H); 7.5 (m, 1H); 7.65 (m, 2H); 8.65 (m, 1H); 8.75 (m, 1H); 9.05 (s, 1H).

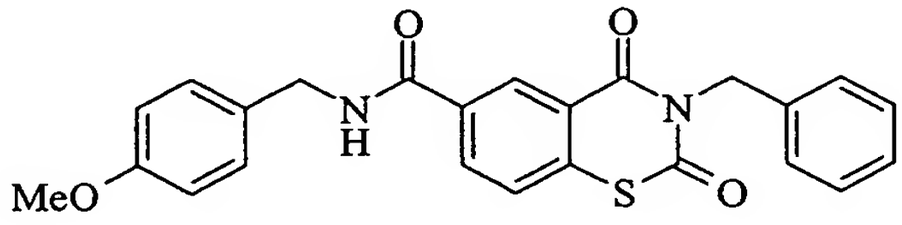
Intermediate F : t-butyl 4-(6-bromo-2,4-dioxo-4*H*-1,3-benzothiazin-3-ylmethyl)-benzoate

A suspension of 6-bromo-3,4-dihydro-benzothiazine-2,4-dione (intermediate E ; 1.5 g, 5.8 mmol) and cesium carbonate (1.89 g, 5.8 mmol) in dimethylformamide (20 ml) was stirred under a nitrogen atmosphere for 0.5 hour at room temperature and treated with 4-(t-butoxycarbonyl)benzyl bromide (1.57 g, 5.8 mmol) ; the mixture obtained was heated at 80°C under stirring and inert atmosphere for 2 hours. The solvent was removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The aqueous layer was reextracted with CH_2Cl_2, the organic phases combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford 2.4 g of crude solid that was purified by chromatography on silica gel (CH_2Cl_2) to give the entitled compound (1.95 g ; yield : 85%) as a white solid pure in TLC (CH_2Cl_2 99/CH_3OH 1 ; Rf = 0.70).

Intermediate G : 4-(6-bromo-2,4-dioxo-4*H*-1,3-benzothiazin-3-ylmethyl)-benzoic acid

A stirred solution of 6-bromo-3-(4-t-butoxycarbonylbenzyl)-3,4-dihydro-benzothiazine-2,4-dione (intermediate F ; 0.6 g, 1.34 mmol) in CH_2Cl_2 (60 ml) was treated at room temperature with trifluoroacetic acid (6 ml). The reaction mixture was stirred overnight at room temperature and poured into water; the resulting insoluble product was isolated by filtration, washed several times until neutral pH and dried under vacuum to afford the entitled acid (0.45 g ; yield : 86%) as a white solid pure in TLC (CH_2Cl_2 95/CH_3OH 5 ; Rf = 0.35).

Example 1 : 3-Benzyl-2,4-dioxo-3,4-dihydro-2H-benzo[e][1,3]thiazine-6-carboxylic acid 4-methoxy benzylamide



To a solution of 25 mg (0.08 mmol) of intermediate C in 2 ml of dimethylformamide, 10.9 mg (0.08 mmol) of 4-methoxybenzylamine and 26 mg (0.08 mmol) of TOTU were added under stirring. After external cooling with ice bath, 20 mg (0.16 mmol) of N,N-

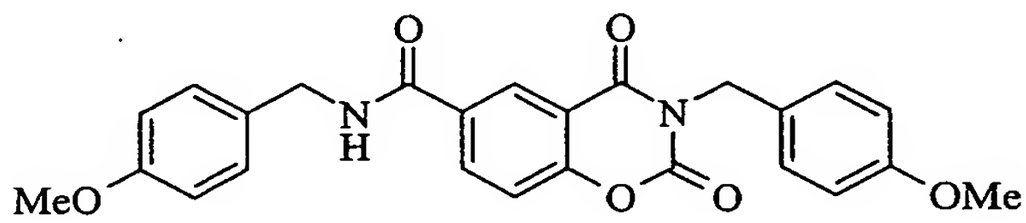
diisopropyl-N-ethylamine were added and the yellow resulting solution was stirred overnight at room temperature. The solvent was removed under vacuum and the residual brown oil was purified by column chromatography over silica gel (dichloromethane then dichloromethane / methanol : 99.5 / 0.5) to yield 13 mg of the desired product (yield : 38%).

N.M.R ($CDCl_3$) ^1H δ (ppm) : 3.8 (s, 3H) ; 4.6 (d, 2H) ; 5.35 (s, 2H) ; 6.5 (s, 1H) ; 6.9 (d, 2H) ; 7.2-7.35 (m, 5H) ; 7.4 (d, 2H) ; 7.5 (d, 2H) ; 8.15 (d, 1H) ; 8.6 (s, 1H).

IR : 1649, 1543, 1514, 1406, 1284, 1253, 1231, 1185, 1145, 1030, 824, 731 cm^{-1}

HPLC : Purity = 96%

Example 2 : 3-Benzyl-2,4-dioxo-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carboxylic acid 4-methoxy benzylamide



A cooled solution of N, N'-bis-(4-methoxybenzyl)-4-hydroxyisophthalic acid (intermediate D, 0.42 g, 1 mmol) in pyridine (5 ml) and acetonitrile (3 ml) was treated with ethyl chloroformate (0.12 g, 1.1 mmol) under stirring and the mixture was heated at 120°C for 8 hours under a nitrogen atmosphere. Further ethyl chloroformate was added (1.1 ml) and the mixture heated at 120°C overnight under stirring. After cooling to room temperature, the reaction mixture was poured into diluted hydrochloric solution and the product extracted several times with dichloromethane. The joined organic phases were washed with diluted hydrochloric solution, diluted solution of sodium hydroxide and brine successively and dried over Na_2SO_4. The solvent was evaporated and the residue triturated in dichloromethane; the insoluble solid is filtrated and dried to afford the entitled compound (0.32 g ; yield : 71%) as a white solid pure in TLC (CH_2Cl_2 95/methanol ; Rf = 0.40).

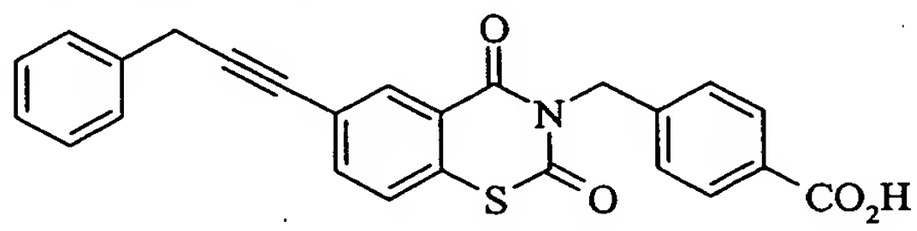
N.M.R (DMSO-d_6) ^1H δ (ppm) : 3.7 (s, 6H); 4.4 (d, 2H); 6.8-6.9 (m, 4H); 7.25 (d, 2H); 7.3 (d, 2H); 7.5 (d, 1H); 8.25 (d, 1H); 8.5 (s, 1H); 9.25 (t, 1H).

IR : 1759, 1693, 1638, 1513, 1446, 1327, 1305, 1244 cm^{-1}

MP = 157°C

HPLC : Purity = 98.5%

Example 3 : 4-[2,4-Dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1,3-benzothiazin-3-ylmethyl]-benzoic acid



6-bromo-3-(4-carboxybenzyl)-3,4-dihydro-benzothiazine-2,4-dione (Intermediate G) (0.39 g ; 0.994 mmol) in dimethylformamide (4 ml) was stirred at room temperature under nitrogen atmosphere and N-ethyl-N,N-diisopropylamine (0.51 g, 3.97 mmol) was added ; the mixture was stirred until complete solubilisation. At this time, 3-phenylprop-1-yne (0.16 g ; 1.39 mmol) was added followed by $PdCl_2(PPh_3)_2$ (30 mg) and a catalytic amount of CuI. The mixture obtained was heated to 50°C under nitrogen atmosphere and maintained under stirring for 3 hours. After cooling, the solvent was removed under reduced pressure and the semi-solid residue obtained was stirred in a mixture of water and dichloromethane for 25 minutes. The solid insoluble in the 2 phases was isolated by filtration, washed with CH_2Cl_2 and dried under vacuum to afford a first portion (0.16 g) of the entitled compound. The organic phase was separated, washed with brine, dried over Na_2SO_4 and evaporated to give an additional portion (0.23 g) of the desired compound (yield 92%).

N.M.R (DMSO-d_6) ^{1}H δ (ppm) : 3.94 (s, 2H); 5.23 (s, 2H); 7.27 (t, 1H); 7.37 (t, 2H); 7.40-7.50 (m, 4H); 7.67 (d, 1H); 7.84-7.95 (m, 2H); 8.23 (s, 1H); 12.75-13.05 (m, 1H).

IR : 1690, 1638, 1425, 1408, 1341, 1318, 1297, 1286, 1181, 1149, 913, 768, 726, 707 cm^{-1}

MP = 240-242°C

HPLC : Purity = 98%

PHARMACOLOGICAL STUDIES OF COMPOUNDS OF THE INVENTION

Example 4 : Evaluation of the in vitro activity of the MMP-13 inhibitor compounds according to the invention.

The inhibitory activity of the compounds of formula (I) according to the invention with respect to matrix metalloprotease-13 is evaluated by testing the ability of the compounds of the invention to inhibit the proteolysis of a peptide substrate with MMP-13.

The peptide substrate used in the test is the following peptide: Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt.

The inhibitory activity of a compound of formula (I) according to the invention is expressed as the IC_{50} value, which is the concentration of inhibitor for which an inhibition of 50% of the activity of the matrix metalloprotease under consideration is observed.

To carry out this test, a reaction medium of 100 µl volume is prepared, containing: 50 mM of HEPES buffer, 10 mM of $CaCl_2$ and 1 mM of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), and 100 µM of substrate, the pH being adjusted to 7.0.

Increasing concentrations of the inhibitory compound present in a 2.0% DMSO solution and 2.5 nM of the catalytic domain of human MMP-13 are added to the test samples.

The concentrations of inhibitors present in the test samples range from 100 µM to 0.5 nM.

The measurement of the proteolysis of the substrate peptide is monitored by measuring the absorbance at 405 nm using a spectrophotometer for reading microplates, at the laboratory temperature, the measurements being carried out continuously for 10 to 15 minutes.

The IC_{50} values are calculated from a curve in which the percentage of the catalytic activity relative to the control is represented on the X-axis and the concentration of inhibitor is represented on the Y-axis.

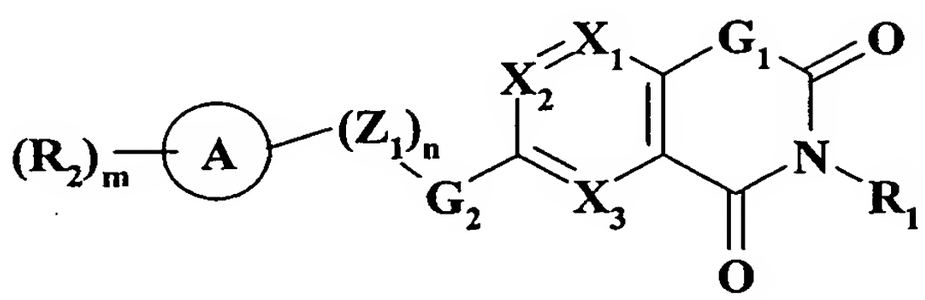
The IC_{50} values on MMP-13 of the compounds of Examples 1 to 3 are all below 0.1 µM.

The test described above for the inhibition of MMP-13 was also adapted and used to determine the ability of the compounds of formula (I) to inhibit the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

The results obtained show that the compounds according to the invention generally have IC_{50} values for MMP-13 which are about 100 times lower than the IC_{50} values for the same compounds with respect to the other matrix metalloproteases tested.

CLAIMS

1- A compound selected from those of formula (I):



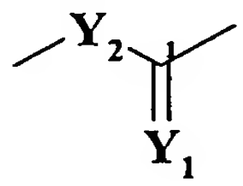
(I)

wherein:

- X_1, X_2, and X_3, independently of each other, represent a nitrogen atom or a group $-CR_3$ in which R_3 represents a group selected from hydrogen, (C_1-C_6)alkyl, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, hydroxy, (C_1-C_6)alkoxy, and halogen, with the proviso that not more than two of the groups X_1, X_2 and X_3 simultaneously represent a nitrogen atom,

- G_1 represents an oxygen atom or a group $S(O)_p$ in which p represents an integer from 0 to 2 inclusive,

- G_2 represents a group selected from carbon-carbon triple bond, C=O, C=S, $S(O)_q$ in which q represents an integer from 0 to 2 inclusive, or a group of formula (i/a):



(i/a)

in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents a group selected from oxygen, sulphur, -NH and $-N(C_1-C_6)$alkyl, and Y_2 represents a group selected from oxygen, sulphur, -NH and $-N(C_1-C_6)$alkyl,

- n represents an integer from 0 to 6 inclusive,

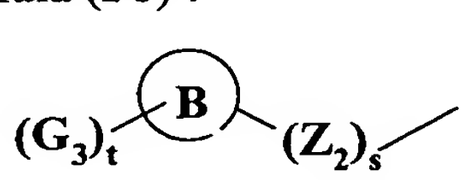
- Z_1 represents $-CR_4R_5$, wherein R_4 and R_5, identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety

is identical or different, $-OR_6$, $-SR_6$, and $-C(=O)OR_6$, in which R_6 is hydrogen atom or (C_1-C_6)alkyl, and

- wherein when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one to two isolated or conjugated multiple bonds,
- and/or wherein when n is greater than or equal to 2 one of said $-CR_4R_5$ may be replaced with a group selected from oxygen, $S(O)_r$ in which r represents an integer from 0 to 2 inclusive, -NH and $-N(C_1-C_6)$alkyl,

- A represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

- R_1 represents a group selected from :
  - hydrogen,
  - (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, these groups may be optionally substituted with one or more groups, which may be identical or different independently of each other, selected from amino, cyano, trihalogeno(C_1-C_6)alkyl, cycloalkyl, $-C(=O)NR_7R_8$, $-C(=O)OR_7$, OR_7, and SR_7, in which R_7 and R_8, which may be identical or different independently of each other, represent hydrogen or (C_1-C_6)alkyl,
  - and the group of formula (i/b) :



(i/b)

  ✓ in which s is an integer from 0 to 8 inclusive,

  ✓ Z_2 represents $-CR_9R_{10}$ wherein R_9 and R_{10}, identical or different independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, phenyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, OR_6, SR_6 and $-C(=O)OR_6$ in which R_6 is as defined hereinbefore, and
  - wherein when s is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or two isolated or conjugated multiple bonds,

- and/or wherein when p is greater or equal to 2, one of said $-CR_9R_{10}$ may be replaced with a group selected from oxygen, $S(O)_u$ in which u is an integer from 0 to 2 inclusive, -NH, $-N(C_1-C_6)$alkyl, and carbonyl,

✓ B represents a group selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, these groups being a 5- or 6-membered monocycle, or bicycle itself composed of two 5- or 6-membered monocycles,

✓ t is an integer from 0 to 7 inclusive,

✓ the group(s) G_3, which may be identical or different independently of each other, is (are) selected from (C_1-C_6)alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{11}R_{12}$, $-N(R_{11})C(=O)R_{12}$, $-N(R_{11})C(=O)OR_{12}$, $-N(R_{11})SO_2R_{12}$, $-N(SO_2R_{11})_2$, $-OR_{11}$, $-S(O)_{k1}R_{11}$, $-SO_2-N(R_{11})-(CH_2)_{k2}-NR_{12}R_{13}$, $-(CH_2)_kSO_2NR_{11}R_{12}$, $-X_4(CH_2)_kC(=O)OR_{11}$, $-(CH_2)_kC(=O)OR_{11}$, $-C(=O)O-(CH_2)_{k2}-NR_{11}R_{12}$, $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{14}$, $-X_4(CH_2)_kC(=O)NR_{11}R_{12}$, $-(CH_2)_kC(=O)NR_{11}R_{12}$, $-R_{15}-C(=O)OR_{11}$, $-X_5-R_{16}$, and $-C(=O)-R_{17}-NR_{11}R_{12}$ in which :

- X_4 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by a hydrogen or a (C_1-C_6)alkyl group,

- k is an integer from 0 to 3 inclusive,

- k1 is an integer from 0 to 2 inclusive,

- k2 is an integer from 1 to 4 inclusive,

- R_{11}, R_{12} and R_{13}, which may be identical or different independently of each other, are selected from hydrogen and (C_1-C_6)alkyl,

- R_{14} represents a group selected from (C_1-C_6)alkyl, $-R_{17}-NR_{11}R_{12}$, $-R_{17}-NR_{11}-C(=O)-R_{17}-NR_{12}R_{13}$, and $-C(=O)O-R_{17}-NR_{11}R_{12}$ in which R_{17} represents a

a linear or branched (C_1-C_6)alkylene group, and R_{11}, R_{12} and R_{13} are as defined hereinbefore,

- R_{15} represents a (C_3-C_6)cycloalkyl group,

- X_5 represents a group selected from a single bond, -CH_2-, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,

- R_{16} represents a group selected from :
  - a 5- or 6-membered monocyclic aryl or heteroaryl, which is optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C_1-C_6)alkyl, halogen, hydroxy, cyano, tetrazolyl, amino, and -C(=O)OR_7 wherein R_7 represents hydrogen or (C_1-C_6)alkyl,
  - and a 5- or 6-membered monocyclic cycloalkyl or heterocycloalkyl, which is optionally susbstituted by one or more groups, which may be identical or different indepently of each other, selected from (C_1-C_6)alkyl, halogen, hydroxy, oxo, cyano, tetrazolyl, amino, and -C(=O)OR_7 wherein R_7 represents hydrogen or (C_1-C_6)alkyl,

- m is an integer from 0 to 7 inclusive,

- the group(s) R_2, which may be identical or different independently of each other, is (are) selected from (C_1-C_6)alkyl, halogen, -CN, -NO_2, -SCF_3, -CF_3, -OCF_3, -NR_7R_8, -OR_7, -SR_7, -SOR_7, -SO_2R_7, -$(CH_2)_kSO_2NR_7R_8$, -$X_7(CH_2)_kC(=O)OR_7$, -$(CH_2)_kC(=O)OR_7$, -$X_7(CH_2)_kC(=O)NR_7R_8$, -$(CH_2)_kC(=O)NR_7R_8$, and –X_8-R_{18} in which:
  - X_7 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,
  - k is an integer from 0 to 3 inclusive,
  - R_7 and R_8, which may be identical or different independently of each other, are selected from hydrogen and (C_1-C_6)alkyl,

- X_8 represents a group selected from single bond, $-CH_2-$, oxygen, sulphur optionally substituted by one or two oxygen, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,

- R_{18} represents a group selected from phenyl, a 5- or 6-membered monocyclic, heteroaryl, and a 5- or 6-membered monocyclic cycloalkyl, each of these groups being optionally substituted by one or more groups, which may be identical or different independently of each other, selected from (C_1-C_6)alkyl, halogen, hydroxy and amino,

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts,

it being understood that :

- an aryl group denotes an aromatic monocyclic or bicyclic system containing from 5 to 10 carbon atoms, and in the case of a bicyclic system, one of the ring of which is aromatic in character, and the other ring of which may be aromatic or partially hydrogenated ;

- a heteroaryl group denotes an aryl group as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen ;

- a cycloalkyl group denotes a monocyclic or bicyclic system containing from 3 to 10 carbon atoms, these systems being saturated or partially unsaturated but without aromatic character ;

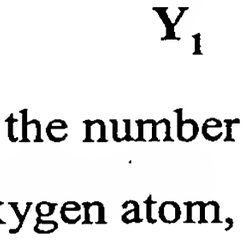
- a heterocycloalkyl group denotes a cycloalkyl group as defined hereinbefore in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur, and nitrogen,

- and a bicycle denotes two fused-monocycle;

and with the proviso that the compound of formula (I) is not 6-(2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine)-benzoate, 6-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine and 6-(2,4-dihydroxy)-benzophenone-2,4-dioxo-3,4-dihydro-2H-1,3-benzothiazine.

2- A compound according to claim 1 wherein :

- G_1 represents a sulphur atom,
- G_2 represents a group of formula (i/a):



(i/a)

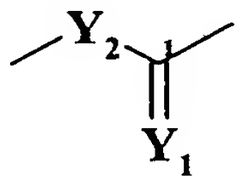
in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- X_1, X_2, X_3, n, Z_1, A, R_1, m and R_2 are as defined in formula (I),

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

3- A compound according to claim 1 wherein :

- G_1 represents an oxygen atom,
- G_2 represents a group of formula (i/a):



(i/a)

in which the carbon atom with the number 1 is attached to the bicycle of the compound of formula (I), Y_1 represents an oxygen atom, and Y_2 represents a group -NH,

- X_1, X_2, X_3, n, Z_1, A, R_1, m and R_2 are as defined in formula (I),

and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

4- A compound according to claim 1 wherein :

- G_1 represents a sulphur atom,
- G_2 represents a carbon-carbon triple bond,
- n represents an integer from 1 to 6 inclusive,

X_1, X_2, X_3, Z_1, A, R_1, m and R_2 are as defined in formula (I),

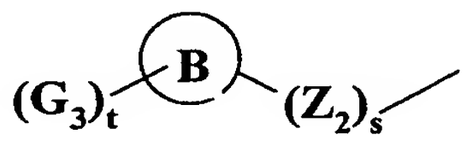
and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

5- A compound according to claim 1 wherein :

- G_1 represents an oxygen atom,
- G_2 represents a carbon-carbon triple bond,
- n represents an integer from 1 to 6 inclusive,

X_1, X_2, X_3, Z_1, A, R_1, m and R_2 are as defined in formula (I),
and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

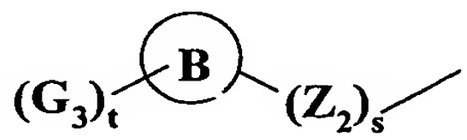
6- A compound according to claim 1 wherein R_1 represents a group of formula (i/b):



(i/b)

wherein Z_2, s, B, G_3 and t are as defined in the compound of formula (I),
and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

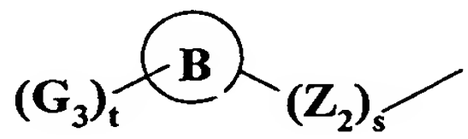
7- A compound according to claim 6 wherein R_1 represents a group of formula (i/b):



(i/b)

wherein Z_2 represents a group $-CR_9R_{10}$ in which R_9 and R_{10} represents each a hydrogen atom, s is equal to one, and B, G_3, and t are as defined in the compound of formula (I),
and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

8- A compound according to claim 7 wherein R_1 represents a group of formula (i/b):



(i/b)

wherein B represents a phenyl group, t is equal to 0 or 1, and G_3, when it is present, represents a group selected from OR_{11}, halogen, and $(CH_2)_kC(=O)OR_{11}$ in which R_{11} represents an hydrogen atom or a $(C_1$-$C_6)$alkyl group and k is equal to zero,
and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

9- A compound according to claim 1 wherein X_1 represents a group $-CR_3$ in which R_3 represents a hydrogen atom, X_2 represents a nitrogen atom or a group $-CR_3$ in which R_3 represents a hydrogen atom, and X_3 represents a group $-CR_3$ in which R_3 represents a hydrogen atom, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

10- A compound according to claim wherein Z_1 represents $-CR_4R_5$ in which R_4 and R_5 represent each a hydrogen atom, and n is equal to one, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

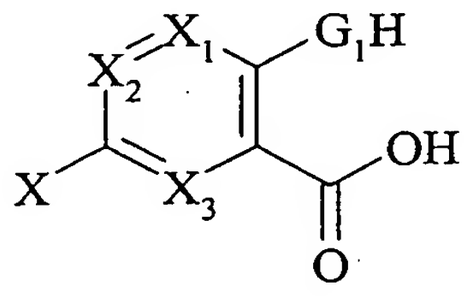
11- A compound according to claim 1 wherein A represents a group selected from phenyl and pyridyl, m is equal to zero or one, and R_2 represents a $(C_1\text{-}C_6)$alkoxy group or a hydrogen atom, and optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

12- A compound according to claim 1 wherein A represents an imidazolyl group, optionally, its racemic forms, isomers, N-oxides, and pharmaceutically acceptable salts.

13- A compound according to claim 1 selected from:

- 3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]thiazine-6-carboxylic acid 4-methoxy benzylamide;
- 3-(4-methoxybenzyl)2,4-dioxo-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine-6-carboxylic acid 4-methoxybenzylamide;
- and 4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1,3-benzothiazin-3-ylmethyl]-benzoic acid.

14- A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II):



(II)

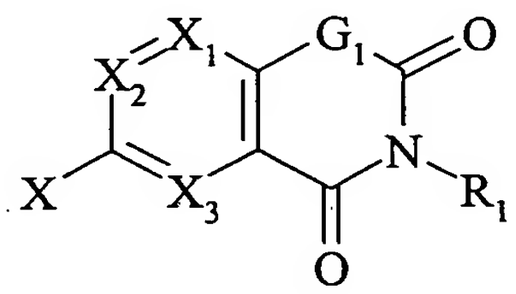
in which X_1, X_2, X_3, and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesyslate, tosylate and SO_2alkyl,

compound of formula (II) which is treated in basic medium with an isocyanate compound of formula (III):

$$R_1\text{-NCO} \qquad \text{(III)}$$

in which R_1has the same definitions as the compound of formula (I),

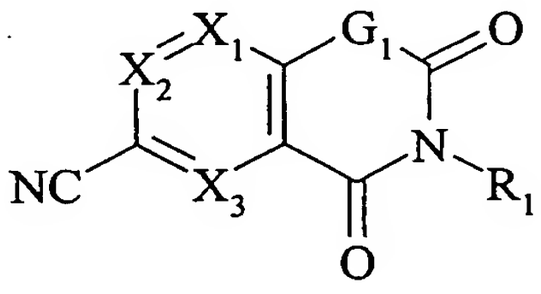
to yield the compound of formula (IV) :



(IV)

in which X_1, X_2, X_3, G_1, X, and R_1 are as defined hereinbefore,

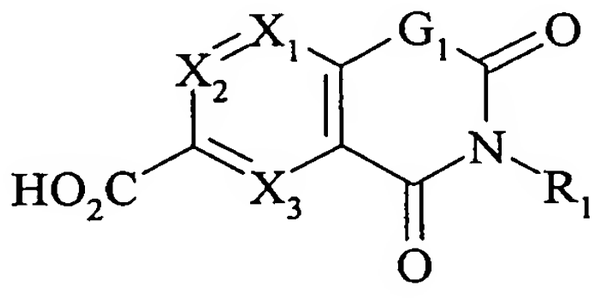
compound of formula (IV) in which the leaving group X is reacted with a cyanocuprate to yield the compound of formula (V) :



(V)

in which X_1, X_2, X_3, G_1, and R_1 are as defined hereinbefore,

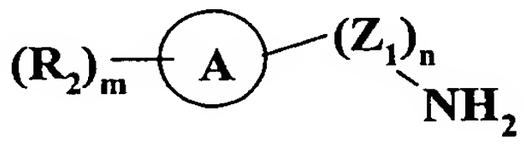
which compound of formula (V) is treated with an acid like sulfuric acid to yield the compound of formula (VI):



(VI)

in which X_1, X_2, X_3, G_1, and R_1 are as defined hereinbefore,

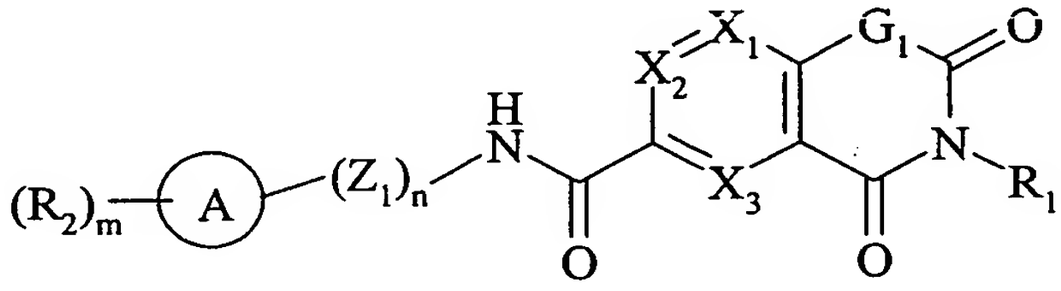
compound of formula (VI) which is treated with a compound of formula (VII):



(VII)

in which Z_1, R_2, A, n and m have the same definitions as the compound of formula (I),

by activating the acid function with an activator, in the presence of diisopropylethylamine and a solvent, to yield the compound of formula (I/a) which is a particular case of the compounds of formula (I):

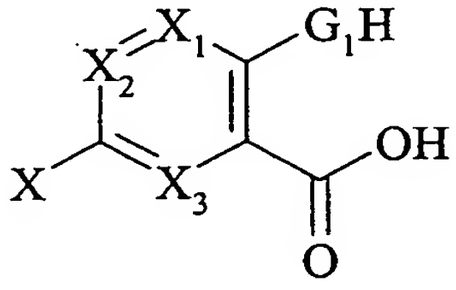


(I/a)

in which X_1, X_2, X_3, G_1, Z_1, R_1, R_2, A, n and m are as defined hereinbefore,

compounds of formula (I/a) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

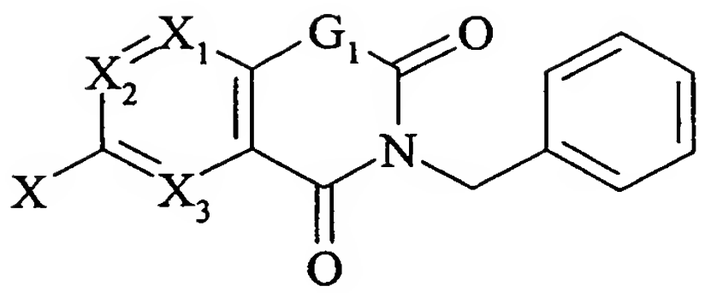
15- A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II):



(II)

in which X_1, X_2, X_3, and G_1 have the same definitions as the compound of formula (I), and X represents a leaving group selected from halogen, triflate, mesyslate, tosylate and SO_2alkyl,

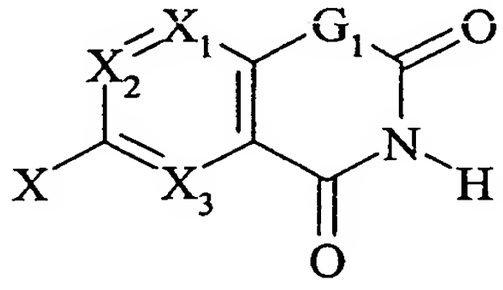
compound of formula (II) which is treated in basic medium with a benzylisocyanate to yield the compound of formula (VIII) :



(VIII)

in which X_1, X_2, X_3, G_1, and X are as defined hereinbefore,

compound of formula (VIII) which is treated with $AlCl_3$ in an apolar solvent to yield the compound of formula (IX) :



(IX)

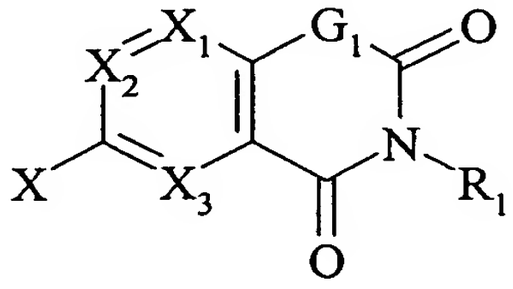
in which X_1, X_2, X_3, G_1, and X are as defined hereinbefore,

which compound of formula (IX) is treated in the presence of an inorganic base with a compound of formula (X):

$$R_1\text{-}X' \qquad (X)$$

in which R_1 is as defined in the compound of formula (I) and X' represents a leaving group like halogen atom, mesylate, tosyslate or triflate group,

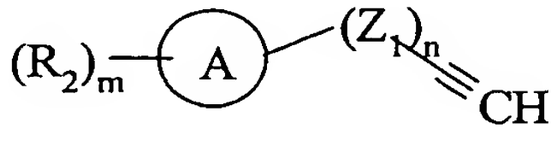
to yield a compound of formula (XI) :



(XI)

in which X_1, X_2, X_3, G_1, X and R_1 are as defined hereinbefore,

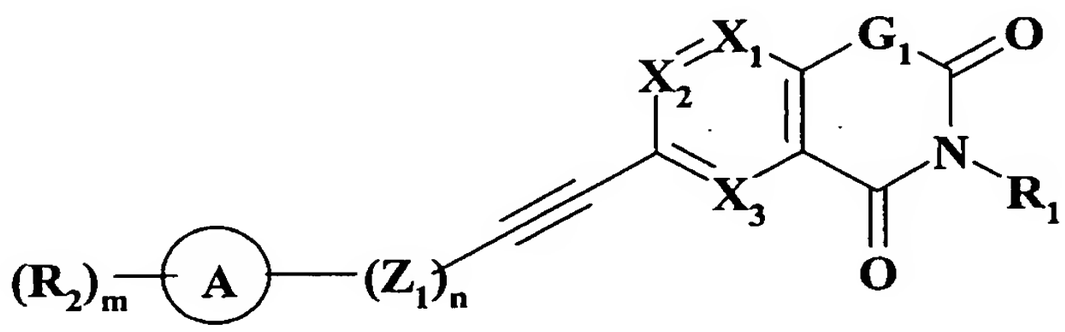
compound of formula (XI) which is condensed, in the presence of dichlorobis(triphenylphosphine)palladium, cupper iodide and *N,N'*-diisopropylethylamine in dimethylformamide, on a compound of formula (XII) :



(XII)

in which Z_1, R_2, A, n and m have the same definitions as the compound of formula (I),

to yield the compound of formula (I/b), which is a particular case of the compound of formula (I):

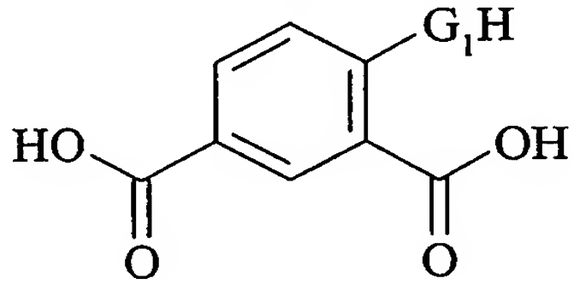


(I/b)

in which X_1, X_2, X_3, G_1, Z_1, R_1, R_2, A, n and m are as defined hereinbefore,

compounds of formula (I/b) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

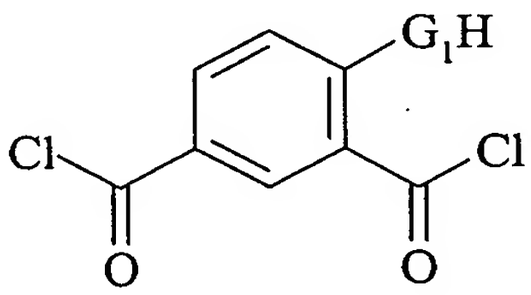
16- A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II/A):



(II/A)

in which G_1 has the same definitions as the compound of formula (I),

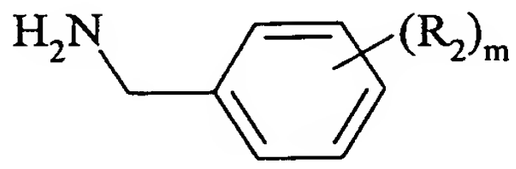
compound of formula (II/A) which is treated with $SOCl_2$ to yield the compound of formula (III/A) :



(III/A)

in which G_1 is as defined hereinbefore,

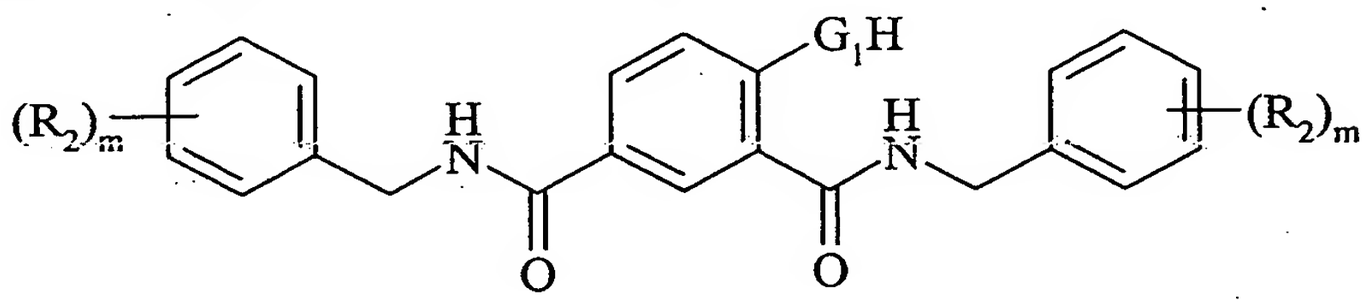
compound of formula (III/A) reacting with a benzylamine derivative of formula (IV/A):



(IV/A)

in which R_2 and m are as defined in the compound of formula (I),

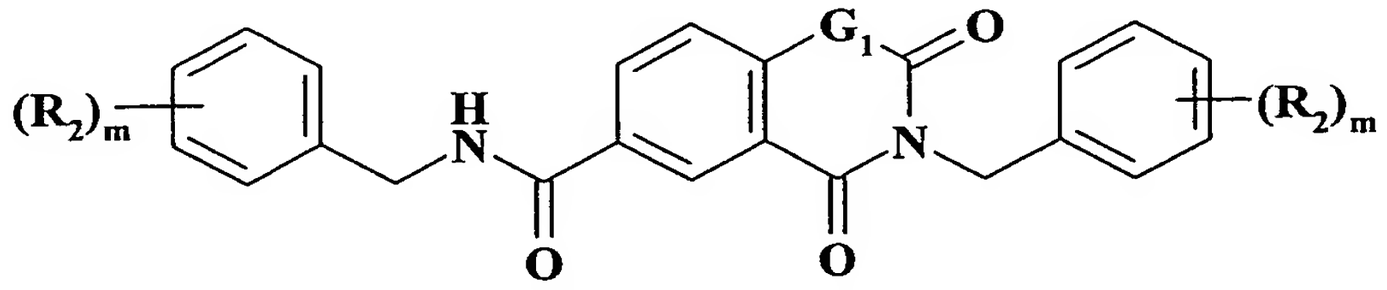
to yield the compound of formula (V/A):



(V/A)

in which G_1, m and R_2 are as defined hereinbefore,

compound of formula (V/A) reacting with a chloroformate compound, to yield the compound of formula (I/c) which is a particular case of the compounds of formula (I):



(I/c)

in which G_1, R_2 and m have the same definitions as the compound of formula (I),

compounds of formula (I/c) constitute some compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base, or into N-oxide thereof.

17- A method for treating a living body afflicted with a disease where the inhibition of type -13 matrix metalloprotease is involved, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

18- A method for treating a living body afflicted with a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel

disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

19- A pharmaceutical composition comprising as active ingredient an effective amount of a compound as claimed in claim 1, alone or in combination with one or more pharmaceutically-acceptable excipients or carriers.

20- A pharmaceutical composition useful in the method of Claim 17 comprising as active ingredient an effective amount of a compound as claimed in claim 1, together with one or more pharmaceutically-acceptable excipients or carriers.

21- A pharmaceutical composition useful in the method of Claim 17 comprising as active ingredient an effective amount of a compound as claimed in claim 2, together with one or more pharmaceutically-acceptable excipients or carriers.

22- A pharmaceutical composition useful in the method of Claim 17 comprising as active ingredient an effective amount of a compound as claimed in claim 4, together with one or more pharmaceutically-acceptable excipients or carriers.

23- Use of a compound according to Claim 1, for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of type-13 matrix metalloproteases.

24- Use according to Claim 23, characterized in that the disease is arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers.

25- Use according to Claim 24, characterized in that the disease is arthritis.

26- Use according to Claim 24, characterized in that the disease is osteoarthritis.

27- Use according to Claim 24, characterized in that the disease is rheumatoid arthritis.